PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 15270C-4-2PC	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 08/80382	International filing date *(day/month/year)* 17 October 2008 (17.10.2008)	(Earliest) Priority Date *(day/month/year)* 17 October 2007 (17.10.2007)
Applicant ELAN PHARMA INTERNATIONAL LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. _____

   ☐ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/80382

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of:

   a. type of material
   - [x] a sequence listing
   - [ ] table(s) related to the sequence listing

   b. format of material
   - [ ] on paper
   - [x] in electronic form

   c. time of filing/furnishing
   - [x] contained in the international application as filed
   - [ ] filed together with the international application in electronic form
   - [ ] furnished subsequently to this Authority for the purposes of search

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/80382

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-9 and 61-63
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I claim 1- 3, 10-60, and 64-133 are directed to a method of treating Alzheimer's disease, and related diseases relative to the absence of ApoE4 alleles.

Group II claims 134-136 are directed to humanized form of a 10D5 antibody.

Group III claims 137-139 are directed to a humanized form of a 12A11 antibody.

Group IV claims 140-142 are directed to a humanized form of a 3D6 antibody.

**********Continued in extra sheet**********

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1- 3, 10-60, 64-133, 143, and 145-146

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/80382

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/00; C07K 16/18 (2009.01)
USPC - 424/133.1, 530/387.3
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 39/00; C07K 16/18 (2009.01)
USPC - 424/133.1, 530/387.3; 424/130.1, 424/141.1, 530/387.3, 530/350, 530/300

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - A61K 39/00; C07K 16/18 (2009.01) - see keyword below
USPC - 424/133.1, 530/387.3; 424/130.1, 424/141.1, 530/387.3, 530/350, 530/300 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Medline, Google
Search terms: Alzheimer's ApoE4 alleles, ApoE4 non-carrier, apolipoprotein E, zero, beta-amyloid, antibody, N-terminal, epitope, mg/kg, intravenous, infusion, ?g/ml, 3D6 antibody, PTA-5130, bapineuzumab, pg/ml, plasma concentration, PTA-5130, vasogenic edema

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y A	US 2006/0280743 A1 (BASI et al.) 14 December 2006 (14.12.2006), para [0005], [0012], [0035], [0057], [0074], [0099], [0105], [0114], [0171], [0172], [0174], [0199], [0201], [0204], [0208], [0209], [0215], [0216], [0217], [02210], [0232], [0238], [0248], [0274], [0335], [0337], [0350], and [0363]	1-3, 10-13, 15-21, 23-25, 27-28, 30-32, 97-98, 101-103, 111-116, 121, 128-131, 133, 145-146 --- 14, 22, 26, 29, 33-60, 64-87, 89-95, 99, 104, 106-108, 110, 117-119, 123-127, 132 --- 88, 96, 100, 105, 109, 120, 122, 143
Y	US 2007/0196375 A1 (TOBINICK) 23 August 2007 (23.08.2007), para [0019], and [0267]	14, 22, 26, 48, 60, 66-70, 87, 94-95, 99, 104, 108
Y A	Kinnecom et. al. Course of cerebral amyloid angiopathy?related inflammation. Neurology. 2007 April. Vol. 68(17), p. 1411-6. Abstract; pg 1411, para 2 and 3; pg 1415, col 1, last para (abstract included to establish publication date)	29, 33-60, 64-87, 89-95, 106-108, 110, 117-119, 123-127, 132 --- 88, 96, 100, 105, 109, 120, 122, 143

☒ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 March 2009 (08.03.2009)	25 MAR 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/80382

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2006/0193850 A1 (WARNE et al.) 31 August 2006 (31.08.2006), para [0149]; SEQ ID NO: 1 and 2	88, 96, 100, 105, 109, 120, 122, 143
A	Aylward et al. Cerebellar volume in adults with Down syndrome. Arch Neurol. 1997 Feb;54(2):209-12. Abstract	1-3, 10-60, 64-133, 143, 145-146
A	Kofke et al. Remifentanil-Induced Cerebral Blood Flow Effects in Normal Humans: Dose and ApoE Genotype. Neurosurg Anesthes Neurosci. July 2007, Vol. 105(1),p.167-175.	1-3, 10-60, 64-133, 143, 145-146

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/80382

Continuation of

Box No. III (unity of invention is lacking)

Group V claim 143 is directed to a humanized antibody comprising a humanized light chain having an amino acid sequence comprising SEQ 10 NO:48 and a humanized heavy chain having an amino acid sequence comprising SEQ ID NO:66 or SEQ ID NO:67.

Group VI claim 144 is directed to an isolated nucleic acid having a sequence comprising SEQ ID NO:68 provided that residues 1-57 encoding a signal sequence mayor may not be present.

Group VII claims 145-146 are directed to an isolated humanized antibody comprising a mature light chain variable region sequence of SEQ ID NO:2 and a mature heavy chain variable region sequence of SEQ ID NO:3, and a human heavy chain constant region of IgG isotype with L234A, L235A, and G237A mutations, wherein positions are numbered by the EU numbering system.

Group VIII claims 147-148 are directed to an isolated humanized form of a 12B4 antibody, wherein the 12B4 antibody is characterized by a light chain variable region sequence of SEQ ID NO:31, and heavy chain variable region sequence of SEQ ID NO:32, and a human heavy chain constant region of IgG isotype with L234A, L235A, and G237A mutations, wherein positions are numbered by the EU numbering system.

Group IX claims 149-151 are directed to a humanized form of a 266 antibody (ATCC accession number PTA6123) comprising a human heavy chain constant region with L234A, L235A and G237A mutations, wherein positions are numbered by the EU numbering system.

Group X claims 152-160 are directed to an isolated antibody comprising a human heavy chain constant region of isotype IgGI, wherein amino acids at positions 234, 235, and 237 (EU numbering) are each alanine.
Group XI claims 161- 193 are directed to a method and a kit for determining a regime for bapineuzumab administration.

Group XII claims 194-195 are directed to a method for improving the safety of bapineuzumab.

The shared technical feature of Groups I, XI and XII is identifying patients having no ApoE4 alleles exhibiting various brain diseases, including, inter alia, Alzheimer's disease. However, this is not an improvement over the prior art of US 5773220 A to DeKoskey et al. (30 June 1998) that specifically teaches identifying patients having no ApoE4 alleles exhibiting various brain diseases, including, inter alia, Alzheimer's disease (abstract, col 2 ln 5-20). Groups II-X are directed to various polypeptide sequences and/or nucleic acid sequences that share no common technical feature with each other or with Groups I, XI and XII, and do not relate to a single general inventive concept because, under PCT Rule 13.2, the different nucleotides or polypeptides represented by the nucleic acid sequences or amino acid sequences are not common to one another but are different because they are composed of unique structural sequences.

Note that Claim Nos. 4-9 and 61-63 have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.